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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER

KERR, KATHLEEN M

ART UNIT PAPER NUMBER

1652

DATE MAILED: 01/27/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary

Application No.

09/851,650

Applicant(s)

BARR ET AL.

Examiner

Kathleen M Kerr

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-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --
Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 16 December 2004.
- 2a) ☒ This action is **FINAL**. 2b) ☐ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 1,3,5,6,8,10,12-14,40 and 41 is/are pending in the application.
- 4a) Of the above claim(s) _____ is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 1,3,5,6,8,10,12-14,40 and 41 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some * c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
 2. ☐ Certified copies of the priority documents have been received in Application No. _____.
 3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- | | |
|---|---|
| 1) <input type="checkbox"/> Notice of References Cited (PTO-892) | 4) <input type="checkbox"/> Interview Summary (PTO-413)
Paper No(s)/Mail Date. _____ |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948) | 5) <input type="checkbox"/> Notice of Informal Patent Application (PTO-152) |
| 3) <input checked="" type="checkbox"/> Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08)
Paper No(s)/Mail Date <u>12/16/04</u> . | 6) <input type="checkbox"/> Other: _____ |

DETAILED ACTION

Application Status

1. In response to the previous Office action, a non-final rejection (mailed on April 29, 2004), Applicants filed a response and amendment (October 29, 2004). Said amendment cancelled Claims 16, 30-34, 37, and 39 and amended Claims 1, 8, 10, 12-14, and 40-41. Thus, Claims 1, 3, 5, 6, 8, 10, 12-14, 40-41 are pending in the instant Office action and will be examined herein.

Priority

2. The instant application is granted the benefit of priority for provisional application 60/033,193 filed on December 18, 1996, non-provisional applications 08/989,332 filed in December 11, 1997 and 09/422,073 filed on October 21, 1999.

Information Disclosure Statement

3. The information disclosure statement filed on December 16, 2004 has been reviewed, and its references have been considered as shown by the Examiner's initials next to each citation on the attached copy. The search report has been considered but is crossed through so as not to appear on the face of any patent related to the instant application.

Withdrawn - Objections to the Specification

4. Previous objection to the specification for lacking complete continuity data in the first paragraph is withdrawn by virtue of Applicant's filing an amended application data sheet altering

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the priority claim to no longer include PCT/US97/23014. Thus, the first paragraph of the specification as filed on July 18, 2002 is appropriate.

5. Previous objection to the specification for not fully complying with the sequence rules is withdrawn by virtue of Applicant's amendment.

Withdrawn – Claim Rejections - 35 U.S.C. § 112, second paragraph

6. Previous rejection of Claim 10 under 35 U.S.C. § 112, second paragraph, as being indefinite for the phrase “expression system for a cell-based detection system ... [for] a polyketide responsive target for a polyketide” is withdrawn by virtue of Applicant's amendment to the language suggested by the Examiner in the previous Office action.

7. Previous rejection of Claims 1, 3, 5, 6, 8, 10, 12-14, 16, 30-34, 37, and 39-41 under 35 U.S.C. § 112, second paragraph, as being indefinite for the abbreviations “KS” and “AT” is ~~withdrawn by virtue of Applicant's amendment defining said abbreviations upon their first~~ appearance in the claims.

8. Previous rejection of Claims 1, 3, 5, 6, 8, 10, 12-14, 16, and 40-41 under 35 U.S.C. § 112, second paragraph, as being indefinite for the phrase “comprising...an ACP activity” is withdrawn by virtue of Applicant's amendment to “an ACP domain” which is clear based on the art.

9. Previous rejection of Claims 32, 37 and 39-41 under 35 U.S.C. § 112, second paragraph, is withdrawn by virtue of Applicant's cancellation and/or amendment of said claims.

10. Previous rejection of Claims 33 and 34 under 35 U.S.C. § 112, second paragraph, is withdrawn by virtue of Applicant's cancellation of said claims.

11. Previous rejection of Claim 40 under 35 U.S.C. § 112, second paragraph, as being indefinite for the phrase "derived from *Bacillus*" is withdrawn by virtue of Applicant's amendment.

Maintained or New – Claim Rejections - 35 U.S.C. § 112, second paragraph

12. Previous rejection of Claims 13-14 under 35 U.S.C. § 112, second paragraph, as being indefinite in the requirement of "different" PKSs is maintained. Applicant's arguments have been fully considered but are not deemed persuasive. Applicant argues that in several locations in the specification, it is clear. However, the Examiner finds no definition of "different" in these sections and Applicant refrains from any remarks concerning the necessity of using modules from naturally occurring, distinct PKSs.

Since the specification is *replete* with examples of mixing and matching PKS domains, modules, and ORFs, it is not unreasonable to require particular clarity in this term. Specifically, Claim 12 requires production of a minimal modular PKS from a cell containing at least two vectors, a first expressing a first module said PKS and a second expressing a second module of said PKS; Claim 13 then requires the first and second modules to be of a first and second PKS respectively, wherein the first and second PKSs are "different". However, as previously noted:

"Is this intended to include PKSs with a single amino acid change, but otherwise the same? PKSs not naturally associated with each other? PKSs from different gene cluster all together? PKSs from different organisms?"

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Consider for example that the DEBS PKS could be modified in its fifth module - consider this a first PKS DEBS [*5]. The DEBS PKS could also be modified in its sixth module - consider this a second PKS DEBS [*6]. One could then take the first module from DEBS[*5] and the second module from DEBS[*6] to produce the claimed host cell wherein the first modules of these two “different” PKSs are identical to each other. It is not hard to see how the term “different” is confusing with such engineering envisioned in the specification. Clarification is required.

13. Previous rejection of Claim 14 under 35 U.S.C. § 112, second paragraph, as being indefinite for, the phrase “encoding a ketoreductase (KR) activity” is maintained. Applicant’s arguments have been fully considered but are not deemed persuasive. Applicant argues that the amendment has obviated the rejection. While the Examiner agrees that this rejection is obviated, a related one is raised. The language now indicates that the nucleotides encode other proteins having KR, DH, ER, and/or TE activities. More appropriate language would indicate that the modules further contain KR, DH, ER, and/or TE domains; such language would be clear.

14. (New) Claims 8, 10, and 12-14 are rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The combination of a, b, and c with conjunctions “and” and “or” is confusing as to whether only b and c are “or-ed” together. Proper structure is required to indicate that item c is always required while one of a or b is also required.

15. (New) Claims 40 and 41 are rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which

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applicant regards as the invention. Said claims depend from Claim 16, which is cancelled.

Clarification is required.

Withdrawn – Claim Rejections - 35 U.S.C. § 112, first paragraph

16. Previous rejection of Claims 8, 10, and 12-14 under 35 U.S.C. § 112, first paragraph, scope of enablement, because the specification, while being enabling for host cells that natively produce polyketides to recombinant produce polyketides in the absence of a holo ACP synthase expression system, does not reasonably provide enablement for host cells that do not natively produce polyketides to recombinant produce polyketides in the absence of a holo ACP synthase expression system is withdrawn by virtue of Applicant's amendment requiring a holo ACP synthase expression system in the instant claims.

Maintained – Claim Rejections - 35 U.S.C. § 112, first paragraph

17. Previous rejection of Claims 1, 3, 5, 6, and 40 (new 8, 10, 12-14) under 35 U.S.C. § 112, first paragraph, written description, is maintained. The instant rejection concerns the lack of written description for host cells or vectors containing expression systems for holo ACP synthases that pantetheinylate a PKS. Claims 8, 10, and 12-14 are added to the instant rejection for the same reasons of record. Applicant's arguments have been fully considered but are not deemed persuasive for the following reasons.

On page 10 of Applicant's remarks, it seems that indefiniteness was considered to be an issue by Applicant's representative; that is not the case. As noted previously, the rejection is one of written description. Applicant also argues one of inoperative embodiments; however, this is

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an issue for enablement which is not the instant rejection. What must be described is the genus of holo ACP synthases claimed - that is, those which pantetheinylate PKSs; this description must be sufficient in structure and function. Applicant further argues the state of the art. The Examiner agrees that Lambalot *et al.* (Chemistry & Biology (1996) 3(11): 923-936) teach ACP synthases; however, what is lacking is a description of the genus claimed - that is only those ACP synthases which pantetheinylate PKSs.

Applicant also argues that the limitation of not being associated with fatty acid synthesis sufficiently further limits the genus. The Examiner disagrees because this is not a structural feature of holo ACP synthases. This is particularly relevant considering Applicant's comments on how HI0152 was previously listed with fatty acids (see Lambalot *et al.*), i.e., excluded from the claimed invention, and now is considered to be useful in the claimed invention. This is precisely why adequate written description is necessary for the claimed invention. The overall amino acid length of holo ACP synthases is not described in the specification as part of the invention, nor is it found in the prior art, and the invention must be adequately described at the time of the invention.

Applicant also argues about selection criterion; the Examiner reiterates that the instant rejection is not one of enablement, but of written description.

18. Claims 1, 3, 5, 6, and 40 (new 8, 10, 12-14) under 35 U.S.C. § 112, first paragraph, scope of enablement, because the specification, while being enabling for EntD, GsP, and sfp as holo ACP synthases that pantetheinylate PKSs, does not reasonably provide enablement for all holo ACP synthases that pantetheinylate PKSs, is maintained. Claims 8, 10, and 12-14 are added to

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the instant rejection for the same reasons of record. Applicant's arguments have been fully considered but are not deemed persuasive for the following reasons.

Applicant argues that the claims are limited to holo ACP synthases that are associated with PKSs; the Examiner disagrees that such a limitation is in the pending claims. The limitation implied is that which excludes holo ACP synthases associated with fatty acid synthesis. As previously noted,

"In the instant specification, no guidance is presented for the purpose of determining expression systems for holo ACP synthases, i.e. determining genes encoding holo ACP synthases, with no discussion of homology among the holo ACP synthases used. The specification teaches three working examples of particular holo ACP synthases, namely, EntD from *E. coli*, Gsp from *B. brevis*, and Sfp from *B. subtilis*, and demonstrate their utility as holo ACP synthases to catalyze a pantetheinyl transfer reaction which converts apo-Acps (inactive) to holo-Acps (active) in the type 1 PKS, DEBS; similar data is also found in Lambalot *et al.* (1996) (see IDS). It is noted that using a holo ACP synthase from *E. coli*, ACPS, with a type I PKS producing erythromycin, DEBS, is not operable for the production of a holo ACP of DEBS. The art involving these holo ACP synthases is not well developed, and thus, the predictability of the art is very low.

While the instant specification describes and enables means for identifying other holo ACP synthases using hybridization methods coupled to activity assays, these methods do not enable one of skill in the art to make all, or a relevant portion of, the expression systems within the scope of the claims because the ability to find a holo ACP synthase gene is not equivalent to the ability to make a holo ACP synthase gene as required by the statute (i.e., "make and use"). No description in the specification or the art provides particular residues whose encoding is important within the genus of holo ACP synthases so that its PKS pantetheinylating behavior is maintained. Thus, one of skill in the art would be unable to predict the structure of the other members of the genus in order to make such members. Therefore, the instant claims are not enabled to the full extent of their scope."

Withdrawn - Claim Rejections - 35 U.S.C. § 102

19. Previous rejection of Claims 1 and 40-41 under 35 U.S.C. § 102(e) as being anticipated by Lambalot *et al.* (USPN 6,579,695) is withdrawn by virtue of the Examiner's reconsideration.

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Reference to *E. coli* by Lambalot *et al.* is only for the overexpression of the holo ACP synthase and not in a co-expression system with PKS.

Withdrawn - Claim Rejections - 35 U.S.C. § 103

20. Previous rejection of Claim 5 under 35 U.S.C. § 103(a) as being unpatentable over Lambalot *et al.* (USPN 6,579,695) is withdrawn by virtue of the Examiner's reconsideration as noted above.

21. Previous rejection of Claims 8, 12-14, 16 and 40-41 under 35 U.S.C. § 103(a) as being unpatentable over Lambalot *et al.* (USPN 6,579,695) in view of Khosla *et al.* (USPN 5,712,146) is withdrawn by virtue of the Examiner's reconsideration as noted above.

Withdrawn - Double Patenting

22. Previous rejection of Claim 3 under 35 U.S.C. § 101 as claiming the same invention as that of claim 3 of prior U.S. Patent No. 6,033,883 is withdrawn. Applicant's arguments have been fully considered but are not deemed persuasive. Applicant argues that the claims have different scope due to the lack of the limitations "wherein the unmodified form does not produce polyketides"; the Examiner disagrees. This limitation is in Claim 1 of USPN 6,033,883.

However, the Examiner has reassessed the scope of the claims in USPN 6,033,883 and recognized that said claim requires a fusion protein between the PKS and the holo ACP synthase (see lines 11-13 of column 18), which fusion protein is not required in Claim 3 of the instant application. The only double patenting rejection might be a non-statutory one which would be obviated by the terminal disclaimer as noted below.

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23. Previous rejection of Claims as shown previously under the judicially created doctrine of double patenting over claims as shown previously of U. S. Patent No. 6,033,883 is withdrawn by virtue of the terminal disclaimer filed on October 29, 2004 disclaiming the terminal portion of any patent granted on this application which would extend beyond the expiration date of USPN 6,033,883 has been reviewed and is accepted. The terminal disclaimer has been recorded.

24. Previous rejection of Claims as shown previously under the judicially created doctrine of double patenting over claims as shown previously of U. S. Patent No. 6,258,566 is withdrawn by virtue of the terminal disclaimer filed on October 29, 2004 disclaiming the terminal portion of any patent granted on this application which would extend beyond the expiration date of USPN 6,258,566 has been reviewed and is accepted. The terminal disclaimer has been recorded.

Summary of Pending Issues

25. The following is a summary of the issues pending in the instant application:

- a) Claims 13-14 stand rejected under 35 U.S.C. § 112, second paragraph, as being indefinite in the requirement of "different" PKSs
- b) Claim 14 stands rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for, the phrase "encoding a ketoreductase (KR) activity".
- c) Claims 8, 10, and 12-14 stand rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for the combination of a, b, and c with conjunctions "and" and "or".
- d) Claims 40 and 41 stand rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for depending from a rejected claim.
- e) Claims 1, 3, 5, 6, and 40 (new 8, 10, 12-14) stand rejected under 35 U.S.C. § 112, first paragraph, written description.
- f) Claims 1, 3, 5, 6, and 40 (new 8, 10, 12-14) stand rejected under 35 U.S.C. § 112, first paragraph, scope of enablement.

Conclusion

26. No claims are allowed for the reasons identified in the numbered sections of this Office action. Applicants must respond to the objections/rejections in each of the numbered sections in this Office action to be fully responsive in prosecution.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See M.P.E.P. § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 C.F.R. § 1.136(a).

A shortened statutory period for reply to this final action is set to expire **THREE MONTHS** from the mailing date of this action. In the event a first reply is filed within **TWO MONTHS** of the mailing date of this final action and the advisory action is not mailed until after the end of the **THREE-MONTH** shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 C.F.R. § 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, ~~will the statutory period for reply expire later than SIX MONTHS from the date of this final~~ action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Kathleen M Kerr whose telephone number is (571) 272-0931. The examiner can normally be reached on Monday through Friday, from 9:00am to 6pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ponnathupura Achutamurthy can be reached on (571) 272-0928. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

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Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).



Kathleen M Kerr
Primary Examiner
Art Unit 1652

January 19, 2005